The Examiner citing PCT Rule 13.1 and 13.2, contends that the species do not relate to a single general inventive concept because they lack the same or corresponding special technical feature *which defines an advance over the prior art.* The Examiner concludes that (i) cyclosporin A, (ii) tacrolimus, and (iii) 33-epi-chloro-33-desoxyascomycin share a significant structural element: formula (I). However, the Office merely cites Wood et al (International Publication No. WO 98/119808, page 7) and asserts that the special technical feature formula (I) does not define a contribution over the prior art, because cyclosporin A is anticipated. However, the Applicants note that cyclosprin A, does not have the "common structural element of formula (I)." Therefore, even if Wood et al does anticipate cyclosporin A, the Examiner has not provided any reason to support restriction between tacrolimus and 33-epi-chloro-33-desoxyascomycin, which *do* share formula (I) as a special technical feature. Accordingly, the Examiner's assertion is without merit and must be withdrawn. Therefore, the criteria for unity of invention *are* satisfied.

Applicants also traverse the Election of Species Requirement on the grounds that the Office has not applied the same standard of unity of invention as the International Searching Authority (see copy of the International Preliminary Examination Report appended herewith). The Authority did not take the position that unity of invention was lacking in the International application and examined all claims together. Applicants note that PCT Article 27(l) states:

> No national law shall require compliance with requirements relating to the form or contents of the international application different from or additional to those which are provided for in this Treaty and the Regulations.

Moreover, Applicants respectfully traverse on the grounds that the Office has not shown that a burden exists in searching the entire application.

MPEP in §803 states as follows:

> If the search and examination of an entire application can be made without a serious burden, the Examiner must examine it on the merits, even though it includes claims to distinct or independent inventions.

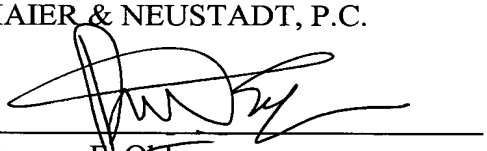
Applicants respectfully submit that a search of all the claims would not impose a serious burden on the Office. In fact, the International Searching Authority has searched all of the claims together.

Therefore, for the reasons presented above, Applicants submit that the Office has failed to meet the burden necessary in order to sustain the Election of Species Requirement. Withdrawal of the Election of Species Requirement is respectfully requested.

Applicants respectfully submit that the above-identified application is now in condition for examination on the merits, and early notice of such action is earnestly solicited

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Attorney of Record
Registration No.: 24,618

Rohitha M. Jayasuriya
Registration No. 50,385

22850

PHONE: (703) 413-3000
FAX: (703) 413-2220
NFO:RMJ

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

TABUSHI, E.
Fujisawa Pharmaceutical Co., Ltd.
Osaka Factory
1-6, Kashima 2-chome, Yodogawa-ku
Osaka-shi
Osaka 532-8514
JAPON

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	29.11.2000
Applicant's or agent's file reference PWO - 18725	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP99/04978	10/09/1999	14/09/1998

Applicant
FUJISAWA PHARMACEUTICAL CO., LTD et. al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Christensen, J Tel.+49 89 2399-8052

Form PCT/IPEA/416 (July 1992)

12.12.-7
12.12.06

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PWO - 18725		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP99/04978	10/09/1999	14/09/1998
International Patent Classification (IPC) or national classification and IPC A61K31/435		
Applicant FUJISAWA PHARMACEUTICAL CO., LTD et. al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03/04/2000	29.11.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Kling, I Telephone No. +49 89 2399 8471

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP99/04978

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-21 as originally filed

Claims, No.:

1-9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-9
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-9
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	1-2 4-6, 8, 9 (see separate sheet section V, 4th paragraph)

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The documents cited in the International Search Report are numbered D1 to D8 in the order of their listing in said Search Report. Unless otherwise indicated, reference is made to the passages cited in said Search Report.

The present application does not satisfy the criterion set forth in Articles 33(2) and 33(3) PCT because the subject-matter of Claims 1 to 9 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT) and does not involve an inventive step (Rule 65(1)(2) PCT).

D1 discloses the effect of an immunosuppressant drug (FK 506 and cyclosporin) on gingival fibroblasts. D2 discloses that the immunosuppressant FK506 selectively inhibits expression of early T cell activation genes. D3 discloses the inhibition of established lesions of collagen-induced arthritis in rats by FK 506. D4 discloses CP-123,369, a potent orally active immunosuppressive agent with efficacity comparable to that of cyclosporin A and FK-506 inhibited human T cell proliferation with an IC_{50} = 10.4nM. D5 discloses the inhibition of interleukin 6 production by adherent rheumatoid synovial cells by FK 506. D7 discloses the effect of FK 506 on arthritis development. D8 discloses the anti-ulcer effect of FK 506 whereas D9 discloses that FK 506 and cyclosporin inhibit growth factor-stimulated human keratinocyte proliferation by blocking cells in the G0/G1 phases of the cell cycle. D10 teaches that the novel ascomycin derivative SDZ ASM 981 is effective for psoriasis when used topically under occlusion (T cell activation is crucial in the pathogenesis of psoriasis). D11 discloses the neuroprotective action of FK506, in experimental stroke. D12, D13 and D14 disclose the effect of tacrolimus hydrate (FK506) on the healing process of experimental gastric ulcers of rats and in the treatment of complicated proximal small bowel and fistulizing Crohn's disease. D15 relates to a drug combination approach to reduce the toxicity of MMP Inhibitor and/or Cyclosporin A administration in particular wherein the cyclosporin is selected from Cy A and FK506. D16 and D17 disclose macrolides of formula (I) as active immunosuppressants and are useful in treating autoimmune diseases such as rheumatoid arthritis and psoriasis in a mammal and for the treatment of resistance to transplantation and fungal infection. D18 discloses a pharmaceutical composition

comprising an immunosuppressive compound selected from Tacrolimus, cyclosporin A, deoxyspergualin or rapamycin or combination thereof. D19 discloses compounds of for mula I which possess interesting pharmacological activity as antiinflammatory, immunosuppressant, antiproliferative and chemotherapeutic drug resistance reversing agents. The compound 33-epi-33chloro-FR 520 (compound of example 66a) is preferred.

For the assessment of the present claims 1-2, 4-6, 8 and 9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment or the subject-matter of claims to a method for the treatment of the human or animal body by therapy or surgery, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

Claim 9 claims at the same time a use, an agent, a method and a pharmaceutical composition and leaves the reader in doubt as to the category of the claim, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).